Study of Non-alcoholic Fatty Liver Disease and its Association with Coronary Artery Disease

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ABSTRACT

Introduction: Non Alcoholic fatty liver disease (NAFLD) is a variety of fatty liver which occurs due to hepatic steatosis, caused by other than excessive alcohol use. Data suggests that NAFLD is also an independent risk factor of cardiovascular disease, which remains the commonest cause of mortality in such patients. This study was conducted to estimate the prevalence of NAFLD diagnosed by ultrasound examination of the liver in type 2 diabetes mellitus (DM). Secondary objective was to demonstrate association between NAFLD and coronary artery disease (CAD) in type 2 DM.

Material and methods: This was an observational study conducted at Department of General Medicine of a tertiary care centre for 2 years. 500 adult patients (age >18 years) of type 2 DM were evaluated for NAFLD, CAD and other cardiovascular risk factors. Microsoft Excel software and SPSS version 20 for Windows were used for data storage and analysis.

Results: The incidence of NAFLD was 44% in all diabetics, among them males were affected more (50%) than females (40%). Mean BMI was 27.8 and 27.2 among males and females respectively. NAFLD subjects had higher incidence of smoking, hypertension, obesity, dyslipidemia, uncontrolled sugar and CAD than Non-NAFLD group subjects. These differences were statistically significant.

Conclusion: We should have high index of suspicion of NAFLD in diabetics. Possibility of NAFLD increases if patients have metabolic syndrome. If found, we should manage risk factors for CAD aggressively as patients have high chances of developing CAD in diabetics with NAFLD.

Keywords: Fatty Liver, Diabetes Mellitus, Coronary Artery Disease

INTRODUCTION

Non Alcoholic fatty liver disease (NAFLD) is a variety of fatty liver which occurs due to hepatic steatosis caused by other than excessive alcohol use. NAFLD is the most common liver disorder in developed countries.[1,2] NAFLD is linked with insulin resistance and metabolic syndrome. It may respond to treatments originally developed for diabetes mellitus type 2 such as weight loss and antidiabetic drugs like metformin and thiazolidinediones.[3] Up to 80% of obese people have NAFLD.[4] Non-alcoholic steatohepatitis (NASH) is the most extreme form of NAFLD, and is regarded as a major cause of cirrhosis of the liver of unknown cause.[5] Most people have a good outcome if the condition is caught in its early stages.[6]

Most people with NAFLD have vague symptoms or no symptoms at all. Patients may complain of easy fatigability, muscle pain, and dull right upper-quadrant abdominal pain. Rarely mild jaundice may be there. Most often NAFLD is diagnosed following abnormal liver function tests during routine blood tests. NAFLD is linked with insulin resistance and metabolic syndrome (obesity, mixed hyperlipidemia, diabetes mellitus, and hypertension). Data suggests that NAFLD is also an independent risk factor of cardiovascular disease, which remains the commonest cause of mortality in such patients. This study was conducted to estimate the prevalence of NAFLD diagnosed by ultrasound examination of the liver in type 2 diabetes mellitus (DM). Secondary objective was to demonstrate association between NAFLD and coronary artery disease (CAD) in type 2 DM.

MATERIAL AND METHODS

This was an observational study conducted at Department of General Medicine of a tertiary care centre. The duration of study was two years; December-2014 to November-2016. Sampling: Subjects were selected by purposive sampling technique after fulfilling inclusion criteria. 500 adult patients (age >18 years) of type 2 DM were evaluated for possible inclusion in this study.

Inclusion criteria: All adults who fulfill criteria of DM by American Diabetes Association criteria or already on treatment for DM were included in this study.

Exclusion criteria: The exclusion criteria were patients of acute or chronic viral hepatitis, history of alcoholism, history of drugs leadind to steatosis (steroids, estrogens, tamoxifen, amiodarone, valproic acid, diltiazem, or methotrexate), patients already on statins, or glitazones, or history of any other chronic liver disease.

Methods: Demographic characters like age, sex, height, waist circumference and weight of all subjects were noted. Detail history was recorded, general physical examination was done and detailed systemic examination was done. Routine investigations including complete blood counts, peripheral smear examination, fasting blood glucose

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(FBG), 2-hr postprandial blood glucose (PPBG), HbA1c, kidney function tests, liver function tests, Lipid profile, and ultrasound of abdomen were done. CAD is diagnosed on the basis of ECG, cardiac enzymes, echocardiography or coronary angiography. All patients underwent ultrasound of the abdomen to detect fatty changes in the liver, performed by a single experienced sonologist. Metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions: FBG>100 mg/dl (or on antidiabetic drug), BP> 130/85 mm Hg (or on antihypertensive drugs), triglycerides >150 mg/dl (or on lipid lowering drugs), HDL-C< 40 mg/dl in men or <50 mg/dl in women (or on lipid lowering drugs), waist circumference≥102 cm in men or ≥88 cm in women. The study was approved by ethical and scientific committee.

STATISTICAL ANALYSIS

Microsoft Excel/ word and SPSS version 20 for Windows were used for data storage and analysis. The quantitative data were expressed as mean ± standard deviation and qualitative data were expressed in percentages and. Student's t test and Chi-Square test were used accordingly to determine statistical difference between variables. Correlations between CAD severity and NAFLD degree were analyzed using Pearson's correlation analysis.

Results:

Total 500 diabetic subjects were included in this study, among them 300 (60%) were female and 200 (40%) were male. Mean age of subjects was 48.8 ±12.8 years.(table 1) Male diabetic subjects had higher incidence of hypertension, dyslipidemia, metabolic syndrome and CAD. The incidence of NAFLD was 44% in all diabetics, among them males were affected more (50%) than females (40%). Mean BMI was 27.8 and 27.2 among males and females respectively. (table 2) NAFLD subjects had higher incidence of hypertension, obesity, dyslipidemia, uncontrolled sugar and CAD than Non-NAFLD group subjects. These differences were statistically significant.(table 3)

On multiple regression analysis, male gender, BMI, raised HbA1c and raised HDL-C did not have influence on the presence of CAD (p>0.05), whereas age [OR:1.03 (95% CI), p=0.002], Smoking [OR:3.28 (95% CI),p=0.006], and NAFLD [OR:2.38 (95% CI), p=0.03] have independent effects.(table 4)

Discussion:

Our results demonstrate that NAFLD is a significant predictor of CAD independent of traditional risk factors in Indians. The prevalence of NAFLD in normal weight individuals without the presence of metabolic risk factors is reported to be around 16%[7] rising to 43-60% in patients with diabetes[8,9], 91% in obese patients undergoing bariatric surgery[10], and up to 90% in patients with hyperlipidaemia.[11,12] The prevalence of NAFLD also increases with age from less than 20% under the age of 20 to more than 40% in over the age of 60[13] and indeed increasing age has been shown to predispose for hepatic steatosis and progression to fibrosis and cirrhosis. The male gender is also a risk factor for progression to NASH and fibrosis.[14] These findings were similar to our study.

Interaction between fatty liver and cardiovascular outcomes have also been evaluated by Wong et al[15] and demonstrated that even fatty liver alone is associated with CAD without other metabolic factors, which is consistent with our results. Association of NAFLD with CAD has also been demostrated by Arslan et al.[16]

The pathogenesis of NASH is currently not well defined but is hypothesized to be complex interactions of environmental and genetics factors. The early 'two-hit' model of NASH has been proposed that the 'first hit' involves accumulation of lipids in the form of triglycerides.[6] This lipid-rich environment then provides the optimum setting for oxidative stress constituting the 'second hit' that triggers hepatocellular injury, inflammation, and fibrosis.

The pathophysiological mechanisms that link NAFLD with CAD are incompletely understood. The concept so far was that in patients with NASH, there was an increase in systemic and hepatic insulin resistance which in turn caused the accumulation of atherogenic dyslipidemia, characterized

Characteristics	Type 2 DM
Number	500
Gender % (Female)	60
Incidence of NAFLD	44%
Age (Mean ± SD)	48.8 ± 12.8 years

Table-1: Demographic measures and biochemical values of All subjects

Characteristics	Male Diabetic Subjects	Female Diabetic subjects
History of Smoking	21%	0%
BMI (Mean ±SD)	27.8 ±4.1 kg/m^2	28.2 ±3.9 kg/m^2
History of Hypertension	45%	42%
FBG (Mean ±SD)	108 ±28.4 mg/dl	105.4 ±19.8 mg/dl
PPBG (Mean ±SD)	220.4 ±94.4 mg/dl	254.3 ±108.5 mg/dl
HbA1c (Mean ±SD)	7.3 ±1.9	7.9 ±2.1
Presence of CAD	12%	11%
LDL-C (Mean ±SD)	139 ±12.9 mg/dl	134 ±21.8 mg/dl
HDL (Mean ±SD)	45.9 ±5.2 mg/dl	42.8 ±6.5 mg/dl
Triglyceride (Mean ±SD)	189.8 ± 20.9 mg/dl	190.2 ±23.9
Presence of Metabolic Syndrome	28%	27%
Incidence of NAFLD	50%	40%

Table-2: Various parameters among male and female diabetics

Characteristics	NAFLD Group	Non-NAFLD Group	P value
History of Smoking	8.3%	7.8%	P=0.09
History of Hypertension	79.3%	22.8%	P<0.005
Incidence of Obesity	87.5%	12.8%	P<0.005
Incidence of dyslipidemia	76.8%	21.3%	P<0.005
HbA1c	8.9 ±2.1	6.9 ±1.9	P<0.005
Incidence of CAD	12.9%	9.8%	P<0.005

Table-3: Various parameters among NAFLD and Non-NAFLD group subjects

	Odds ratio	P value
Age	1.03	0.002
Male Gender	1.48	0.52
Smoking	3.28	0.006
BMI	0.98	0.12
Raised HbA1c	1.32	0.55
Raised HDL-C	0.98	0.18
NAFLD	2.38	0.03

Table-4: Multiple logistic regression analysis for the presence of CAD

by high triglycerides, low HDL and high VLDL. In NASH, there seemed to be increased production of many pro-inflammatory markers such as uric acid and C-reactive protein (CRP)[16], IL-6, TNF-α as well as profibrogenic markers such as tumor growth factor-β, endothelin 1 and insulin like growth factor-1 which can lead to CAD.[17] Epidemiological studies performed in United States and Japan showed that NAFLD is associated with increased risk of CAD and is a predictor of CAD independent of the presence of other metabolic syndrome risk factors such as hypertension, diabetes, dyslipidemia, obesity and insulin resistance.[18] The RISC (Relationship between Insulin Sensitivity and Cardiovascular disease) study showed that patients with NAFLD had an increased 10 year CAD risk score even when only considering those at perceived low risk patients (i.e. without diabetes or hypertension).[19] The study also showed that subjects with NAFLD are more prone to early carotid atherosclerosis in the absence of coexisting metabolic syndrome risk factors.[20] Recent phase II trials have showed that NAFLD patients are more likely to have advanced high risk coronary plaque, independent of traditional cardiovascular risk factors as compared with patients without NAFLD.[21] Patients with stage 3 or 4 fibrosis at baseline had worst prognosis.[22] Perazzo H et al. Showed that patients with even 20% Framingham cardiovascular risk score, the presence of advanced fibrosis was predictive of cardiovascular events.[23]

Mainstay of treatment of NAFLD is weight loss through dietary modification and physical exercise, but practically it is difficult to achieve. Most often we require pharmacological treatment along with life style modifications. Insulin sensitizers drugs like metformin, pioglitazone, and GLP-1 receptor agonists (exenatide) have shown promising results in NAFLD. Other drugs like vitamin E, pentoxifylline, betaine, and ursodeoxycholic acid have also been studied for nafld with little success.

CONCLUSION

We should have high index of suspicion of NAFLD in diabetics. Possibility of NAFLD increases if patients have metabolic syndrome. If found, we should manage risk factors for CAD aggressively as patients have high chances of developing CAD in diabetics with NAFLD.

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